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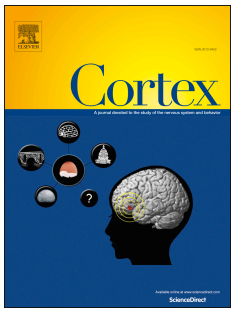

Sources of adaptation of inferior temporal cortical responses

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Abstract.

Neurons of different brain regions change their response when a stimulus is repeated. In inferior temporal cortex (IT), stimulus repetition typically reduces the responses of single neurons, i.e. IT neurons show repetition suppression. Single unit recordings in IT showed that individual neurons vary in their degree of adaptation effects, ranging from strong suppression to slight enhancement of the response to the repeated stimulus. The suppression is maximal after the peak of the response and then reduces during the further course of the response. Repetition suppression in IT is still present for interstimulus intervals of at least 900 ms. I discuss the contribution of mechanisms that have been proposed to explain adaptation effects of IT responses. Firing-rate dependent response fatigue, e.g. a prolonged hyperpolarization, intrinsic to the recorded neuron cannot explain the stimulus specificity of the adaptation effect. The latter can be explained by synaptic depression or an adapted input from other IT neurons. We observed repetition suppression of IT neurons when adapter and test stimuli were presented at locations that differed by 8 degree of visual angle, suggesting that at least part of the adaptation effect is not inherited from retinotopic visual areas with small receptive fields. We observed no effect of repetition probability on repetition suppression in macaque IT using images of various categories, suggesting a dissociation between top-down expectation effects and repetition suppression. Together, our data agree with the hypothesis that adaptation in IT serves to reduce the saliency of recently seen stimuli, highlighting stimuli that differ from recently presented ones.

Keywords: Repetition Suppression; macaques; inferotemporal cortex; repetition probability; stimulus-specific adaptation.

Abbreviations

IT : inferior temporal cortex

Many brain areas of different species show adaptation: their neural response to a stimulus changes after exposure to that stimulus. The sort of adaptation-induced response changes can depend on the area (Weiner, Sayres, Vinberg, and Grill-Spector 2010) and can vary from suppression of the response ("repetition suppression") to enhancement. Repetition suppression is ubiquitous in macaque inferior temporal (IT) cortex, the end-stage of the ventral visual stream. Indeed, several studies showed that the responses of IT neurons usually decrease with stimulus repetition (De Baene and Vogels 2010;Kaliukhovich and Vogels 2011;Kaliukhovich and Vogels 2012;Kaliukhovich and Vogels 2014;Liu, Murray, and Jagadeesh 2009;McMahon and Olson 2007;Miller, Li, and Desimone 1991;Sawamura, Orban, and Vogels 2006;Vogels, Sary, and Orban 1995). This repetition suppression (Desimone 1996) has aroused recent interest because of the widespread use of adaptation paradigms in human fMRI studies (Malach 2012), especially (but not exclusively) in ventral stream areas, some of which are likely homologues of monkey IT cortex. In fact, a highly influential paper that introduced the fMRI-adaptation technique dealt with the invariance of object representations in human occipito-temporal areas (Grill-Spector, Kushnir, Edelman, Avidan, Itzchak, and Malach 1999). Despite criticisms of the fMRI-adaptation technique to infer the stimulus selectivity or invariance of neurons (Sawamura, Orban, and Vogels 2006;Tolias, Keliris, Smirnakis, and Logothetis 2005), fMRI adaptation studies are still being performed and even interpreted as if the stimulus selectivity of adaptation effects directly reflects the tuning of neurons (for a very recent example see Glezer, Kim, Rule, Jiang, and Riesenhuber (2015)). Aside from the relevance for interpreting fMRI adaptation data, the changes in neural responses with adaptation show the impact of stimulus history on the neural representation of a stimulus. Given that stimulus history affects perception (Bar and Biederman 1999;Muller, Schillinger, Do, and Leopold 2009;Noudoost and Esteky 2013), a better understanding of adaptation is necessary to gain a deeper insight into the neural mechanisms of perception (Clifford et al. 2007). Despite the theoretical and practical importance of adaptation, the mechanisms underlying adaptation in IT are still poorly understood.

1. Short-term adaptation: paradigm and phenomenology of adaptation effects.

In this paper, I will discuss the underlying mechanisms of adaptation in macaque IT, relating these to observations made in single unit recording studies. I will discuss mainly short-term adaptation studies, in which the stimuli are presented for relatively short durations (as in most fMRI-adaptation studies) and without intervening stimuli (unlike in "priming" –related studies). It is well possible that the mechanisms of short-term adaptation differ at least to some extent from those underlying adaptation following long-duration exposure to stimuli or with long time delays with intervening stimuli present in-between the adapter and test stimuli. Thus, the adaptation paradigm that I will discuss here consists of 300 to 1000 ms presentations of a stimulus, the adapter stimulus, followed by an interstimulus interval of 300- 1000 ms, after which a second stimulus is presented, the test stimulus. The test and adapter stimuli can be either identical ("repetition trials") or different ("alternation trials"; see Figure 1 for a typical adaptation protocol). The images are presented when the monkeys are fixating a small target. Fixation of the gaze inside a small electronic fixation window (typically 2° on a side) is required for 300-500 ms before and after the stimulus presentations and during the interstimulus interval in order to obtain a juice reward. Trials in which fixation is broken during the trial (aborted trials) are discarded. Analyses of the eye movements inside the fixation window failed to detect a relationship between eye movements and adaptation effects in IT in all studies we have conducted.

An often ignored issue concerns the visual stimulation condition before the adapter stimulus. In some studies, no stimulus, except for an uniformly illuminated display, is presented in the intertrial interval while in other studies stimuli that are supposed to disadapt the neuron are presented. The latter can vary from sequences of spatially scrambled images (e.g. De Baene and Vogels (2010) – to which IT neurons typically respond poorly (Vogels 1999)) – to short presentations of full-screen natural images. We do not know whether adaptation effects would differ without these (e.g. as with an empty interstimulus interval). It should be noted though that for some "passive" adaptation mechanisms – such as response fatigue (see below) – the recent stimulus history before the adapter stimulus will impact the response to the adapter and hence test stimuli. In all but a few studies of

adaptation in IT, the monkeys were awake during the study and the animals were free to make eye movements during the intertrial interval, implying that the intertrial intervals varied between trials and were constrained only by a lower bound. The intertrial intervals in most studies were at least an order of magnitude longer than the interstimulus interval. In most of our studies, we employed pseudorandomized stimulus presentations in which the adapter stimulus of a trial differed in identity from the test stimulus of the previous trial. This pseudorandomization together with the presentation of intervening stimuli and long intertrial intervals serve to reduce adaptation effects of stimuli of the previous trial on the subsequent adapter and test stimuli responses.

The short-term adaptation protocol produces repetition suppression in repetition trials in most – but not all – IT neurons. The adaptation effects can be quantified by computing an adaptation index that normalizes the difference in response to the adapter and the repeated stimulus by the response to the adapter stimulus. An adaptation index of 0.5 indicates that the response to the repeated stimulus was half the response to the adapter, while a negative adaptation index indicates an enhancement of the response to the repeated stimulus following the adapter. Typically, the response strength for a stimulus is computed as the average firing rate in a window that equals the stimulus duration but that is delayed by 50 ms to allow for the minimal response latency of IT neurons. One can compute the adaptation indices for raw responses (average firing rate computed inside the window) or for baseline-subtracted net responses. Baseline subtraction will not affect the sign of the adaptation index but will affect its magnitude: adaptation indices computed on net firing rates are larger than those obtained with raw responses because in the latter case one divides by a larger number. This should be taken into consideration when comparing adaptation indices between studies. Figure 2 shows distributions of the adaptation index obtained for single unit net responses in two IT studies, employing different sorts of stimuli (De Baene and Vogels 2010;Sawamura, Orban, and Vogels 2006). In both studies, the single unit recordings were made in anterior IT (TE). The stimulus duration and interstimulus interval was 300 ms. The stimuli were familiar to the monkeys and were selected to effectively drive the neurons in an independent test. Otherwise, no selection

was performed. It is clear that, on average, IT neurons show repetition suppression: the response is less for the repeated stimulus compared to the same stimulus shown as an adapter. On the other hand, there is also a considerable variability in the degree and sign of the adaptation effects between the different neurons recorded in a single study. One possible explanation of the measured variation in adaptation between neurons is that it merely reflects measurement noise. I tested this hypothesis by a re-analysis of the data of the Sawamura study (Sawamura, Orban, and Vogels 2006) in which the adaptation of each single neuron was tested with two effective stimuli (their "A" and "B" images). I correlated the adaptation indices obtained in repetition trials for the two different effective stimuli, i.e. the A-A and B-B presentations. If the between-neuron variation in the degree of adaptation was merely due to measurement noise, than no significant correlation between the adaptation indices for the two stimuli would be present. However, the Pearson correlation coefficient r was 0.53 and significantly higher than 0 ($P < 0.00001$; $n = 169$ neurons), indicating that at least part of the variation in the adaptation indices reflect real neuron-to-neuron variation that is stimulus independent. Note that this neuron-to-neuron variation of the degree of adaptation was unrelated to the effectiveness of the stimuli, since, as reported before by Sawamura and colleagues, there was no significant correlation between the adaptation index for a stimulus and its firing rate to the adapter ($r = 0.002$, n.s.; $n = 169$). De Baene and Vogels (2010) found no differences between the adaptation indices of neurons located in the anterior ventral bank of the Superior Temporal Sulcus and in the convexity lateral to the Anterior Middle Temporal Sulcus. Whether neurons with similar adaptation indices cluster on a smaller scale in IT is unclear. Kaliukhovich and Vogels (2012) found no systematic differences in the degree of adaptation of multi-unit activity sampled with a laminar electrode at different laminae of the anterior ventral bank of the Superior Temporal Sulcus, suggesting that both upper and deeper layers of at least that part of IT show adaptation.

Figure 3 plots the peristimulus time histograms of the responses to the adapter and test stimuli obtained in the same two studies (De Baene and Vogels 2010;Sawamura, Orban, and Vogels 2006). As pointed out by Liu et al (2009), the short-term adaptation effect in IT is not stationary

during the course of the response. Repetition suppression increases after response onset and then declines during the later stage of the response. Notably, the response to the repeated stimulus shows typically a dip roughly between 160 and 220 ms after stimulus onset. Models of adaptation effects in IT should be able to explain this peculiar time course of repetition suppression in IT cortex.

The adaptation effects in IT are readily obtained with a single repetition of a stimulus. More repetitions increase the degree of suppression, relative to the first presentation of the stimulus (Figure 4). However, the degree of repetition suppression scales nonlinearly with the number of repetitions, with the first repetition demonstrating the strongest suppressive influence. How repetition number interacts with stimulus duration and the interstimulus interval at the single unit level in IT remains to be investigated.

2.1. Response fatigue.

The mechanism initially thought to underlie repetition suppression and commonly assumed in accounts of fMRI adaptation is spike frequency-dependent "fatigue" or "response fatigue": firing spikes will decrease the firing rate of the neuron during subsequent stimulation. Such spiking-dependent suppression has been demonstrated in the primary visual cortex of cats (Sanchez-Vives, Nowak, and McCormick 2000a;Sanchez-Vives, Nowak, and McCormick 2000b). In these studies, it was shown that an artificial membrane depolarization that produced a spike train was sufficient to reduce the firing rate for a subsequent equal depolarization. One mechanism underlying this reduced excitability, which is fully intrinsic to the neuron, is a prolonged afterhyperpolarization that involves sodium and calcium dependent potassium channels. The afterhyperpolarization is modulated by acetylcholine through muscarinic receptors (for review, see Thiele (2013)) and thus can be affected by vigilance or the cortical state of the animal. Because muscarinic receptor density differs between areas and between animal species (Thiele 2013), it is difficult to generalize data obtained in other areas of other species to IT of awake behaving monkeys. Interestingly, single neurons of cat area 17 varied considerably in the strength of the afterhyperpolarization for equal stimulation strengths

(Sanchez-Vives, Nowak, and McCormick 2000b), which may underlie the marked differences in the degree of repetition suppression between IT neurons. In these studies in the primary visual cortex, the afterhyperpolarization followed a seconds long membrane depolarization and thus it is an open question whether the short adapter durations employed in IT are sufficient to induce a sufficiently strong afterhyperpolarization. Thus this is a rather slow adaptation mechanism (time constants in seconds) that should not be confused with a much faster spike rate adaptation that occurs within a 300 ms long single stimulation with time constants several orders of magnitude smaller (Ahmed, Anderson, Douglas, Martin, and Whitteridge 1998), which relies on potassium currents that are calcium-dependent.

Response fatigue predicts that the degree of adaptation of a neuron should primarily depend on its spike frequency to the adapter. However, several studies indicated that this prediction does not always hold in IT. Sawamura, Orban, and Vogels (2006) showed that the degree of repetition suppression of single IT neurons differed between two different adapter stimuli that produced equal responses in the neuron. This stimulus-specific adaptation was also demonstrated later with an oddball paradigm (Kaliukhovich and Vogels 2014). Liu, Murray, and Jagadeesh (2009) reported that the degree of repetition suppression did not correlate with the number of spikes fired by the neuron on a trial-to-trial basis. De Baene and Vogels (2010) showed that in some conditions the degree of repetition suppression is even inversely related to the response strength for the adapter. A regression analysis estimating the contribution of a firing rate dependent mechanism to the degree of repetition suppression of single IT neurons suggested that such a mechanism could account only for a small amount of the response variance to the test stimuli in the majority of neurons (De Baene and Vogels 2010). Together these findings suggest that a membrane depolarization-dependent mechanism at the level of the single neuron plays only a minor role in repetition suppression in IT. However, a definite conclusion regarding the contribution of this source of adaptation to IT repetition suppression awaits studies in which the membrane depolarization of IT neurons is directly manipulated in vivo.

2.2 Input fatigue: synaptic depression.

Several single unit studies in IT showed that the relationship between adapter and the subsequent test stimulus is a strong determinant of the degree of suppression: the suppression is the strongest when adapter and test stimuli are identical (De Baene and Vogels 2010;Sawamura, Orban, and Vogels 2006) and decreases with decreasing similarity between the adapter and test stimuli (Verhoef, Kayaert, Franko, Vangeneugden, and Vogels 2008). This stimulus specificity suggested that repetition suppresses the input to the IT neuron, which we labeled "input fatigue" (De Baene and Vogels 2010). The stimulus specificity of the adaptation effect then results from the stimulus selectivity of the synaptic or afferent inputs to the neuron. The degree of cross-adaptation, measured when adapter and test stimuli differ, will depend on the overlap of the adapted input and the input related to the test stimulus.

Input fatigue is a descriptive label that can cover mechanistically different sources. The first possible source is synaptic depression, a short-term synaptic plasticity phenomenon that is mainly presynaptic (for reviews see Fioravante and Regehr (2011); Zucker and Regehr (2002)). Synaptic depression is well-documented in vitro but less prominent in vivo, decreasing with the amount of spontaneous cortical activity in the anesthetized cat primary visual cortex (Reig, Gallego, Nowak, and Sanchez-Vives 2006). Synaptic depression may reflect different molecular mechanisms (Fioravante and Regehr 2011), with time courses that in principle could account for visual adaptation (Chance, Nelson, and Abbott 1998;Finlayson and Cynader 1995). Although a likely contributor to repetition suppression, a causal role of depression of cortico-cortical synapses in repetition suppression in IT has not been demonstrated yet. An evaluation of the contribution of synaptic depression to repetition suppression will necessitate measurements of repetition suppression following manipulation of synaptic depression mechanisms. These studies should ideally be conducted in awake, behaving animals instead of in vitro, since synaptic depression is influenced by the cortical state (Reig, Gallego, Nowak, and Sanchez-Vives 2006) and neuromodulators such as acetylcholine

(Gil, Connors, and Amitai 1997). Furthermore, at least fast synaptic depression may depend on the species, being smaller in magnitude in primates than in rodents (Testa-Silva et al. 2014).

2.3 Input fatigue: suppressed input of other IT neurons.

Instead of or in addition to depressed synapses, another source of input fatigue is suppressed input of other adapted IT neurons to the neuron under study. In this scenario, the suppression does not result from depressed synaptic transmission – as in synaptic depression – but from suppressed neurons through undepressed synapses. As in other cortical areas, IT neurons receive input from other neurons of the same area and this in a not-random patchy manner (Fujita and Fujita 1996). All IT neurons that respond to the adapted stimulus can be expected to become suppressed as a result of e.g. spike-dependent fatigue (see 2.1.; or synaptic depression). Thus, for example, a small spiking-dependent fatigue effect in each of the neurons that respond to the adapter stimulus can become amplified by means of the recurrent connectivity between these adapted neurons, resulting in relatively strong adaptation effect in a single neuron. In such a scheme, the stimulus-specificity of repetition suppression is caused by the stimulus selectivity of the input neurons: two stimuli that can drive equally a particular neuron can nonetheless activate two largely different populations of IT units that can become selectively adapted. In such a scheme, the time course of the adaptation effect, in particular the late onset of the bulk of the adaptation effect (Figure 2), does naturally follow from the suppression being largely caused by recurrent connectivity between IT neurons. Differences in the degree of adaptation between neurons result in such a scheme from the intracortical connectivity of a particular neuron with the rest of the IT network, which can differ between individual cortical neurons (Okun et al. 2015). Although this adapted neuronal input mechanism can explain, at least at face value, the properties of adaptation in IT, direct experimental proof is still lacking.

The above recurrent network view stresses that the adaptation effects observed at the single unit level can result from effects that occur in the network of neurons of which the single

neuron is a part. This network view when expanded to inhibitory, divisive inputs to the neuron, predicts enhancement instead of suppressive effects under particular conditions (Solomon and Kohn 2014). We found that adaptation to an ineffective stimulus enhances the response of single IT neurons to a compound stimulus that consisted of the simultaneous presentation of an effective and the ineffective image (Kaliukhovich and Vogels, Society for Neuroscience Abstracts, 2013). This enhancement can be understood by assuming an adaptation-induced suppression of the divisive normalizing input to the neuron.

2.4. Adaptation effects inherited from early cortical areas.

Before the stimulus reaches IT, it has been processed in several visual cortical areas, e.g. V1, V2 and V4. These areas are known to show adaptation effects. For instance, fMRI adaptation for repeated images of objects, presented in a block design, occurs in all areas along the ventral visual stream in the monkey (Sawamura, Georgieva, Vogels, Vanduffel, and Orban 2005). Few studies however employed short-term adaptation paradigms in early visual cortical areas of awake animals, i.e. brief adapter durations with a (short) interstimulus interval, as is typically employed in IT. Interestingly, a recent study in macaque V1 (Patterson, Wissig, and Kohn 2013) showed that, on average, the adaptation effect measured with a stimulus duration of 400 ms disappeared when the interstimulus interval between adapter and test was only 100 ms, unlike in IT where adaptation is present for much longer interstimulus intervals (Figure 5). Furthermore, usually smaller sized stimuli are employed in early visual areas than in IT, matching the smaller receptive field (RF) sizes in the early areas. However, as shown in elegant work by the Kohn group (Patterson, Wissig, and Kohn 2013;Wissig and Kohn 2012), stimulus size can have a profound effect on adaptation effects in early visual areas because of stimulation of the suppressive surround by larger stimuli. Also, studies in early visual areas suggest that divisive normalization mechanisms can become differentially engaged by complex stimuli, e.g. stimuli containing multiple orientations, which influences and in some instances even abolishes repetition suppression (Wissig and Kohn 2012). Thus, it is imperative that

the same stimuli (and of course the same presentation protocols) are employed when comparing adaptation effects across different areas, but few studies have done so (for exceptions see (Patterson, Duijnhouwer, Wissig, Krekelberg, and Kohn 2014;Patterson, Wissig, and Kohn 2014).

In principle, it is possible that the repetition suppression seen in IT is inherited from adaptation in earlier visual areas (as has been shown to hold for at least some adaptation effects in the dorsal area MT (Patterson, Wissig, and Kohn 2014)). To determine whether the adaptation effects observed in IT might originate in earlier visual areas with small RFs, De Baene and Vogels (2010) presented the adapter and test stimuli at different, non-overlapping locations (at 4° eccentricity above or below the fixation target) within the RF of IT neurons. If adaptation in IT is inherited from such earlier areas, adaptation would be absent when both adapter and test stimuli do not fall within the same RFs at those earlier levels. Significant repetition suppression (median adaptation index : 0.21) was observed when adapter and test stimuli were presented at the different locations, but the degree of suppression was less than when the two stimuli were presented at the same location (0.36;(De Baene and Vogels 2010)). The robustness of repetition suppression even when adapter and test stimulus have different positions suggests that it was, at least partially, generated at a higher-level visual area rather than being inherited from earlier stages with smaller RFs. These results differed from a previous study (Lueschow, Miller, and Desimone 1994) that reported a complete tolerance of repetition suppression to changes in stimulus location of the adapter and test stimuli. This discrepancy between the two studies may be due to differences in recording region (more medial/ventral IT, encroaching perirhinal cortex (Lueschow, Miller, and Desimone 1994) versus lateral IT and ventral bank of the Superior Temporal Sulcus (De Baene and Vogels 2010)) and/or task (passive fixation (De Baene and Vogels 2010) versus a position-invariant recognition task (Lueschow, Miller, and Desimone 1994)).

We (De Baene and Vogels 2010) observed a similar time course of the repetition suppression when the adapter and test stimulus were presented at the same position compared with

presentations at different positions, suggesting that similar mechanisms underlie repetition suppression in both cases. IT RFs are built-up in IT: local application of a GABA-antagonist affects the RF size and organization in IT (Wang, Fujita, Tamura, and Murayama 2002). Hence, the position-dependent component of the suppression may in fact reflect position-dependent synaptic input to the neuron just like object-dependent suppression reflects object-dependent input. In other words, the position-dependent adaptation that we observed can be viewed as just another form of stimulus feature-specific adaptation, with position being a feature just like color, orientation, curvature etc.. This implies that the position-selective component of the adaptation effect may not necessarily demonstrate an inheritance (of that component) from early visual areas.

Finally, I would like to note that the position manipulation employed by De Baene and Vogels only shows that at least part of the adaptation effect is not inherited from early visual cortical areas V1 and V2 (and by implication also the retina and lateral geniculate nucleus) and very likely V4. However, because of the size of stimulus location differences employed in our study, one cannot exclude that the adaptation effects in anterior IT, area TE, were inherited from posterior IT areas (e.g. TEO/PIT), which provide input to TE (Kravitz, Saleem, Baker, Ungerleider, and Mishkin 2013). It would be interesting to bypass the bottom-up processing stages by directly stimulating IT neurons and measure the effect of stimulation repetition on the responses of IT neurons.

3. Attention and adaptation effects

Stimulus-specific adaptation may be related to differences in attention between the adapter and test stimuli: a repeated stimulus may be attended less than a “novel” stimulus and this decreased attention results in a suppressed neural response to the repeated stimulus. Note that this can mean that a repeated stimulus engages less bottom-up, exogeneous attention or that a repeated stimulus will engage less top-down, endogenous attention. The former possibility leads to a chicken and egg problem: is the decreased response caused by a decreased attention or is the decreased response a manifestation or cause of the decreased saliency of the repeated stimulus? I believe the

latter is the case: a potential decreased attention to a repeated stimulus results from adaptation and not vice versa.

To examine the causal contribution of attention to adaptation, we equated attention to the adapted and test stimuli by presenting adaptation sequences when the monkeys performed a "dimming" task in which they were required to detect a subtle global luminance change of the stimuli (De Baene and Vogels 2010). The luminance change could occur for either the test or the adapter image, and was introduced in a small proportion of the trials. Thus, to detect the random luminance changes, the animal was required to attend to both test and adapter stimuli. The animals were trained extensively in this task for several months to reach asymptotic performance. The performance of both monkeys was well below ceiling rate during the recordings (average detection rate 73%) and false-alarm rates were very low (< 1%). In both monkeys, the detection rate of the dimming of the test stimulus did not depend on the shape similarity between the test and the preceding adapter stimulus. Thus, the level of stimulus attention was expected to be similar for the repetition and alternation trials. Nonetheless, significant repetition suppression was present in trials in which no dimming occurred and that were randomly interleaved with the dimming trials, with a median adaptation index of 0.31. The median adaptation index did not differ significantly between the dimming task and when the animals passively fixated during presentation of the stimuli (De Baene and Vogels 2010).

These data suggest that repetition suppression in IT is present when attention to adapter and test stimuli is equated. However, this does not imply that selective attention-related factors cannot modulate adaptation effects in IT. It is well established that stimulus selective, top-down attention affects the responses of IT neurons (Chelazzi, Duncan, Miller, and Desimone 1998;Chelazzi, Miller, Duncan, and Desimone 1993;Desimone 1996), as it does in other visual cortical areas. Such attentional effects are also expected to modulate the IT responses in adaptation protocols. In fact, top-down, attentional modulations can explain the variability in repetition effects that have been

reported when monkeys were performing tasks in which stimulus repetition is relevant to solve the task. We (Vogels and Orban 1994) found marked individual differences in the sign of repetition effects (i.e. suppression versus enhancement) in IT when the animals were performing a temporal same-different task of oriented gratings, with one animal even showing on average an enhancement instead of a suppression of the responses to the repeated stimuli in the "same" trials. Another study (Eskandar, Richmond, and Optican 1992) reported no repetition suppression of the average IT response when the animals were engaged in a temporal same-different task of texture patterns. These differences between animals and studies can be explained by assuming that different animals employed different strategies to solve the task: one strategy by responding to non-matching stimuli which can enhance the response to matching stimuli by a top-down biasing signal and another one that relies on the detection of non-matching stimuli, which will produce repetition suppression. (Miller and Desimone 1994) indeed showed that changing the nature of the task can markedly affect the proportion of IT neurons showing repetition suppression versus enhancement, which likely reflects a change in top-down biasing signals (Desimone 1996). It should be stressed that the demonstration that the task influences IT responses in repetition trials does not imply that repetition suppression is caused by task-related variables. Indeed, repetition suppression is present in IT – and even appears to be stronger – under anesthesia (Miller, Gochin, and Gross 1991), a state in which task-related factors are absent.

4. Adaptation as a manifestation of a reduced prediction error.

A recent alternative model of adaptation stresses the role of top-down factors in generating repetition suppression (Friston 2005;Summerfield, Trittschuh, Monti, Mesulam, and Egner 2008). In that model, repetition suppression is a consequence of the fulfillment of perceptual expectations or of a reduced mismatch between expected and observed percepts, i.e. a reduced prediction error. Thus, repetition suppression should occur when the subject expects that a stimulus will be repeated (low prediction error), and there should be a diminished or no suppression when the repeated

stimulus is unexpected (large prediction error). An influential human fMRI study (Summerfield, Trittschuh, Monti, Mesulam, and Egner 2008) showed indeed that BOLD repetition suppression in the Fusiform Face Area was greater in blocks in which repetition of a face was more frequent than in blocks where repetition was improbable. Thus, the occurrence of repetition suppression in this area depended on stimulus repetition probability, a parameter related to statistical temporal regularities in the flow of visual information across several trials. This strong contextual effect cannot be explained by local network or bottom-up fatigue mechanisms. Because the computation of repetition probability requires the integration of information across several trials, it is also unlikely that repetition probability effects on adaptation depend on local computations in visual cortical areas which very likely have a rather limited temporal integration span. Given the challenge that the Summerfield et al data presents to the above discussed sources of repetition suppression, we decided to examine the effect of repetition probability on adaptation in macaque IT (Kaliukhovich and Vogels 2011). We employed the same timing parameters and repetition probabilities as those in the Summerfield et al fMRI study. Unlike most studies of repetition suppression in macaque IT, but as in the Summerfield et al and most other human fMRI adaptation studies, each trial consisted of "trial-unique", novel stimuli. Contrary to the human fMRI study of Summerfield et al, we found no effect of repetition probability on adaptation in macaque IT. The absence of such an effect held for both spiking activity and local field potentials. Results were similar in 3 monkeys, for artificial fractal and natural stimuli, and were also present when only highly effective stimuli were selected. Despite the absence of a repetition probability effect, we observed stimulus-specific adaptation in each animal and for both stimulus sets. The absence of an effect of repetition probability together with presence of repetition suppression suggested that the repetition suppression in macaque IT is unrelated to repetition probability.

The effects of repetition probability on adaptation has been replicated in several studies in humans since the original Summerfield et al paper (Grotheer, Hermann, Vidnyanszky, and Kovacs 2014;Grotheer and Kovacs 2014;Kovacs, Iffland, Vidnyanszky, and Greenlee 2012;Kovacs, Kaiser,

Kaliukhovich, Vidnyanszky, and Vogels 2013;Larsson and Smith 2012), even with direct EEG measurements (Summerfield, Wyart, Johnen, and de, V 2011) instead of the fMRI BOLD measure which is a rather indirect measure of neural activity to which task-related pure vascular responses can contribute (Sirotin and Das 2009). What then might have caused the absence of any effect of repetition probability in our macaque IT study? One potentially relevant difference between our paradigm and that of Summerfield et al. (and the other fMRI studies) is that our monkeys were performing a passive fixation task while the subjects in the Summerfield et al study were required to detect an inverted or size-deviant face and thus were required to attend to the stimuli. An elegant human fMRI study showed that the effect of repetition probability is not observed when subjects are not attending the stimuli (Larsson and Smith 2012). Importantly, in that study, as in our monkey single unit study, adaptation effects were present despite the absence of an effect of repetition probability, again dissociating repetition suppression and the repetition probability manipulation. In our monkey study, we employed a wide variety of natural images of different categories while Summerfield et al used faces as stimuli. (Kovacs, Kaiser, Kaliukhovich, Vidnyanszky, and Vogels 2013) replicated the effect of repetition probability on fMRI adaptation using faces but the same human subjects did not show an effect of repetition probability when the same stimuli as in the Kaliukhovich and Vogels monkey study were presented. Also, no effect of repetition probability was found for images of chairs. Thus, differences between stimulus categories and not a difference between species or between attentional processes may underlie the discrepancy between the findings in humans and the Kaliukhovich and Vogels monkey study on repetition probability. Interestingly, a subsequent human fMRI study showed a repetition probability effect on adaptation for upright letters of the roman alphabet but not for unfamiliar false fonts (Grotheer and Kovacs 2014). Taken all these studies together suggest that repetition probability effects occur only for highly familiar stimulus categories such as faces and letters. One possible explanation is that such stimuli may automatically engage attention and attention is known to play a role in the expression of the repetition probability effect (see above). Most human fMRI studies that reported an effect of

repetition probability on adaptation found an increased BOLD response in the unexpected alternation trials in blocks with a high probability of repetition trials, compared to the activations seen in blocks with a low repetition probability (see Kovacs and Vogels (2014) for a review). This is not the same as a reduction of the BOLD response for the expected repetition trials compared to alternation trials and in fact corresponds to a "surprise" response to a deviant stimulus.

In summary, so far, there is no direct neurophysiological evidence against the hypothesis that repetition suppression in IT largely reflects bottom-up or local adaptation mechanisms (Figure 6). However, under some conditions the adaptation effects can interact with expectation/surprise related top-down modulations, explaining repetition probability effects observed in some studies, which can range from an increased suppression for repeated, expected stimuli to an enhanced response to unexpected, deviants. One can speculate that the local adaptation mechanisms in IT – and at previous stages – implement a "repetition prior", reflecting the stability of the world across short time scales. However, this concept differs from the "perceptual expectation" or "predictive coding" hypothesis of adaptation which relies on expectation/prediction-related feedback from hierarchically higher regions (Friston 2005).

5. Function of adaptation in IT.

Speculating about the function of adaptation and repetition suppression in IT is difficult given our current lack of a precise understanding of the mechanisms underlying adaptation. However, the known phenomenology of adaptation effects in IT and the effect of adaptation on neural representations can be of help in building a hypothesis about the function of adaptation in IT. Adaptation reduces selectively the response to a stimulus that is identical to the one seen recently. Kaliukhovich, De Baene, and Vogels (2013) showed that the single neuron discriminability of test stimuli was reduced for repeated compared to non-repeated shapes in a short-term adaptation protocol. In some conditions for which adapter and test shapes differed, the cross-adaptation however resulted in an enhanced discriminability. Furthermore, the multi-unit spiking activity of

small neuronal populations showed a decreased classification accuracy for repeated compared to non-repeated test stimuli, but classification was enhanced for the test compared to adapter stimuli when the test stimulus differed from recently seen stimuli (Kaliukhovich, De Baene, and Vogels 2013). The drop in classification accuracy for repeated stimuli in IT implies that these neurons reduce their coding of recently observed stimuli compared to a stimulus that differs from a recently seen one. This might be a sensible strategy for IT, an area which is involved in object identification and categorization, since an object that differs from a recently observed object needs to be identified/categorized in order to produce an adaptive behavioral response but it is less required to identify/categorize de novo a recently seen object. This selective reduction of the response to repeated stimuli can be metabolically opportune. At the same time, the classification of a changed stimulus is efficient and it becomes more salient. Indeed, the adaptation studies in IT together with those in early visual cortex (Solomon and Kohn 2014) suggest that a general role of adaptation is to decrease the saliency of recently seen stimuli. This reduction in saliency of a repeated stimulus has as consequence that a non-repeated stimulus will “pop out”, instigating deeper processing.

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Figure Legends

Figure 1. A typical short-term adaptation protocol. In this example, two stimuli are shown successively, separated by a 300 ms blank field. Two types of trials are presented to the subject: repetition trials (AA) in which the same stimulus is repeated and alternation trials (AB) in which the two stimuli of a sequence differ. The monkey is required to fixate a target (indicated by the red square, for clarity shown larger than in the actual experiments) during the entire trial. The stimulus presentations are preceded by a baseline fixation interval of 500 ms and followed by a post-stimulus fixation period of 450 ms. A juice reward is given, contingent on successful fixation, at the end of the trial period. Repetition trials and alternation trials consist of different stimuli on different trials, chosen to cause a response in the recorded unit as established in an independent test. The intertrial interval is an order of magnitude longer than the interstimulus interval. In the studies reviewed in this paper, the stimulus duration varied between 250 and 500 ms and the interstimulus interval between 300 and 500 ms.

Figure 2. Distribution of adaptation indices of IT neurons. A. Adaptation indices computed on net responses for effective stimuli (selected separately for each neuron). Positive indices indicate repetition suppression, negative repetition enhancement. A two fold decrease of the response to a repeated stimulus corresponds to an adaptation index of (2-1)/2 = 0.5. The adaptation indices (169 single IT neurons of two monkeys) were computed from the data obtained by Sawamura, Orban, and Vogels (2006). Stimuli were color images of natural stimuli (animals, objects etc.). B. Adaptation indices obtained in the study by De Baene and Vogels (2010), based on net responses (n= 77 neurons of two monkeys). Stimuli were artificial shapes. In both studies the stimulus duration and interstimulus interval was 300 ms.

Figure 3. Population peristimulus time histograms of IT responses to the adapter and test stimulus. The mean responses to the adapter and test stimulus are shown in full and stippled lines, respectively. A. Responses were first normalized with respect to the peak firing rate and then

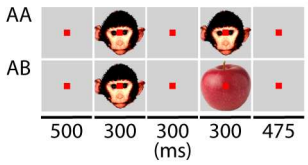
averaged across neurons (n= 169 neurons of two monkeys). The responses were computed from data of the Sawamura, Orban, and Vogels (2006) study. B. Mean firing rate without normalization. Results from the De Baene and Vogels (2010) study (n= 80 neurons of two monkeys). Stimuli were identical to those of the data shown in Figure 2. 0 corresponds to stimulus onset. No smoothing was applied. Bin width 10 ms. In both studies the stimulus duration and interstimulus interval was 300 ms.

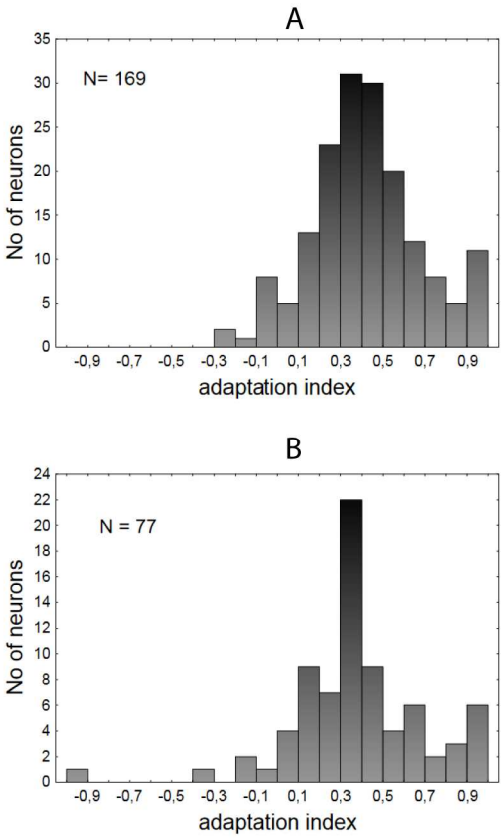
Figure 4. Effect of presentation number on the adaptation effect of IT neurons. Mean responses as a function of the number of stimulus presentations (maximum = 29 repetitions of the same stimulus). Stimulus duration and interstimulus interval was 300 ms. The number of neurons decreased slightly for the higher stimulus presentations (n= 169 neurons or less). Data from Sawamura, Orban, and Vogels (2006). Only responses to the most effective stimuli (out of 30) are shown.

Figure 5. Population peristimulus time histograms of IT responses to the adapter and test stimulus for an interstimulus interval of 600 (top; N = 22 neurons) and 900 ms (bottom; N =21). The stimulus durations were 300 ms. The mean responses to the adapter and test stimulus are shown in full and stippled lines, respectively. Responses were first normalized with respect to the peak firing rate and then averaged across neurons. The responses were computed from data of the Sawamura, Orban, and Vogels (2006) study. 0 corresponds to stimulus onset. No smoothing was applied. Bin width 10 ms.

Figure 6. Schematic and simplified illustration of bottom-up and local network sources of adaptation. Circles represent neurons, left: areas providing input to IT; right: IT. Neurons with different color have different feature tuning. The neuron in black is the one recorded from. It receives direct input from the green colored neurons of the early area as well as lateral input from green colored neurons in IT. In addition, it receives input from a “dark blue” neuron. Connections within IT are bidirectional allowing recurrent interactions. An adaptation effect recorded in the “black” IT neuron can result from firing rate fatigue of that neuron. Such mechanism will produce a

suppression of the response in the recorded neuron when stimulated with features that excite the "dark blue" neuron following adaptation to a stimulus that excites the "green" but not the "dark blue" neurons, i.e. cross-adaptation. Alternatively, adaptation can result from synaptic depression of the input, reducing the synaptic strengths of the direct, afferent input (w(a)) and indirect, lateral input (w(l)). Such mechanism will not produce cross-adaptation in the recorded neuron when stimulated with features that excite the "dark blue" neuron following adaptation to features that depresses the output of the "green" neurons, although both the neuron receives input from both "green" and "dark blue" neuron. Aside from synaptic depression, adaptation can decrease the response of the neurons in the input area and cause an adaptation effect in IT by reducing its input ("inherited adaptation"). Thus, adapting the "green" neurons of the input area will result in a suppressed response of the recorded IT neuron when stimulating the "green" neurons and not when stimulating the "blue" neurons after adaptation. The recorded IT neuron receives inhibitory input from a "light blue" IT neuron. Adapting the response of the latter neuron can cause an enhanced ("disinhibition") instead of a suppressed response in the recorded IT neuron.





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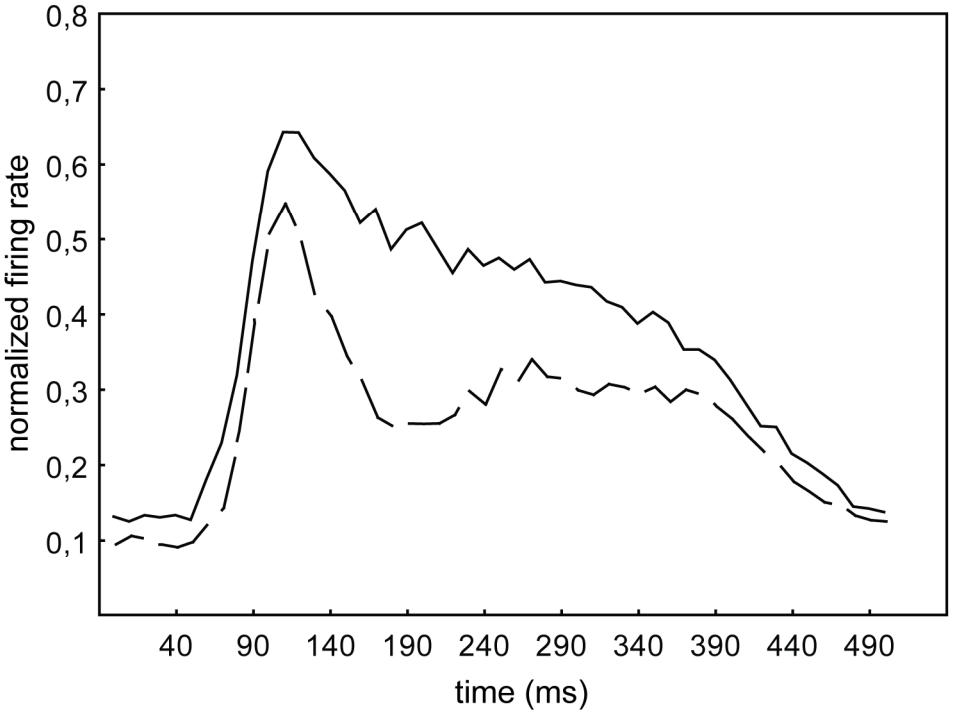
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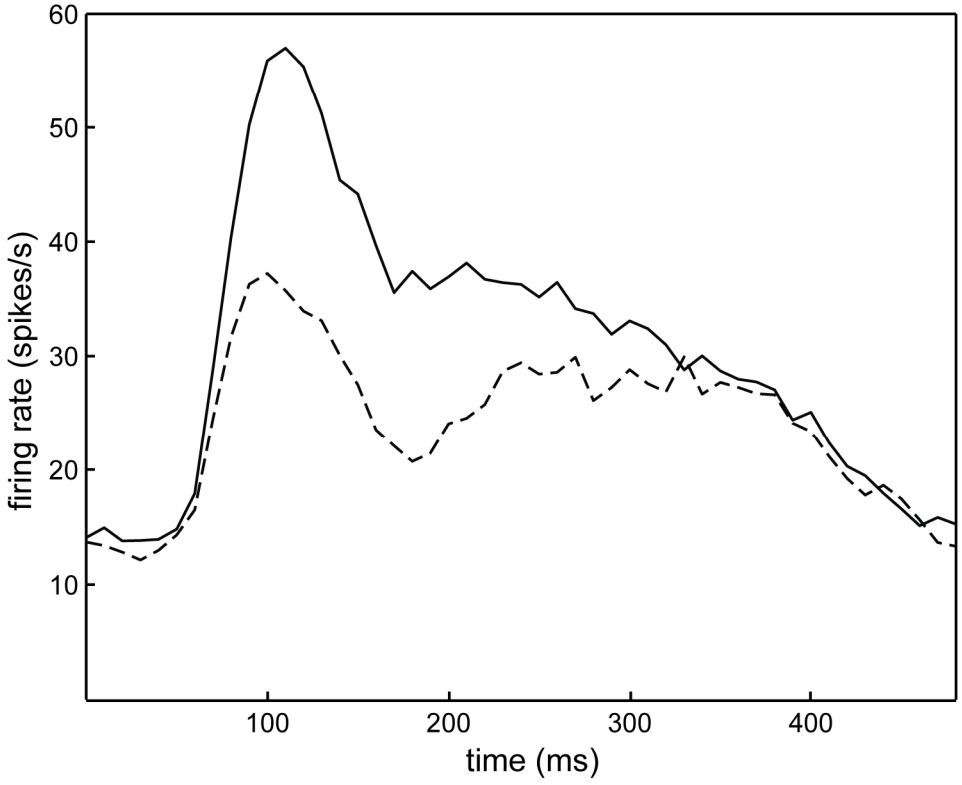
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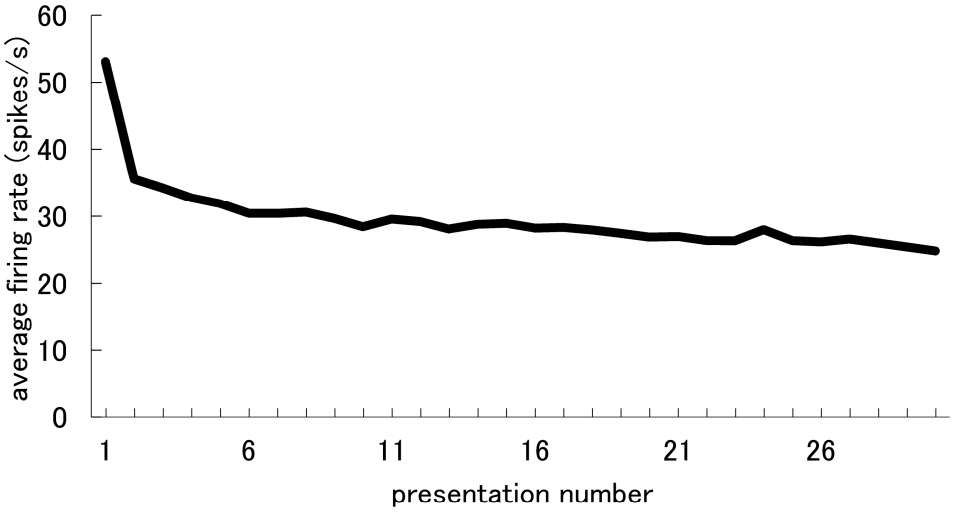

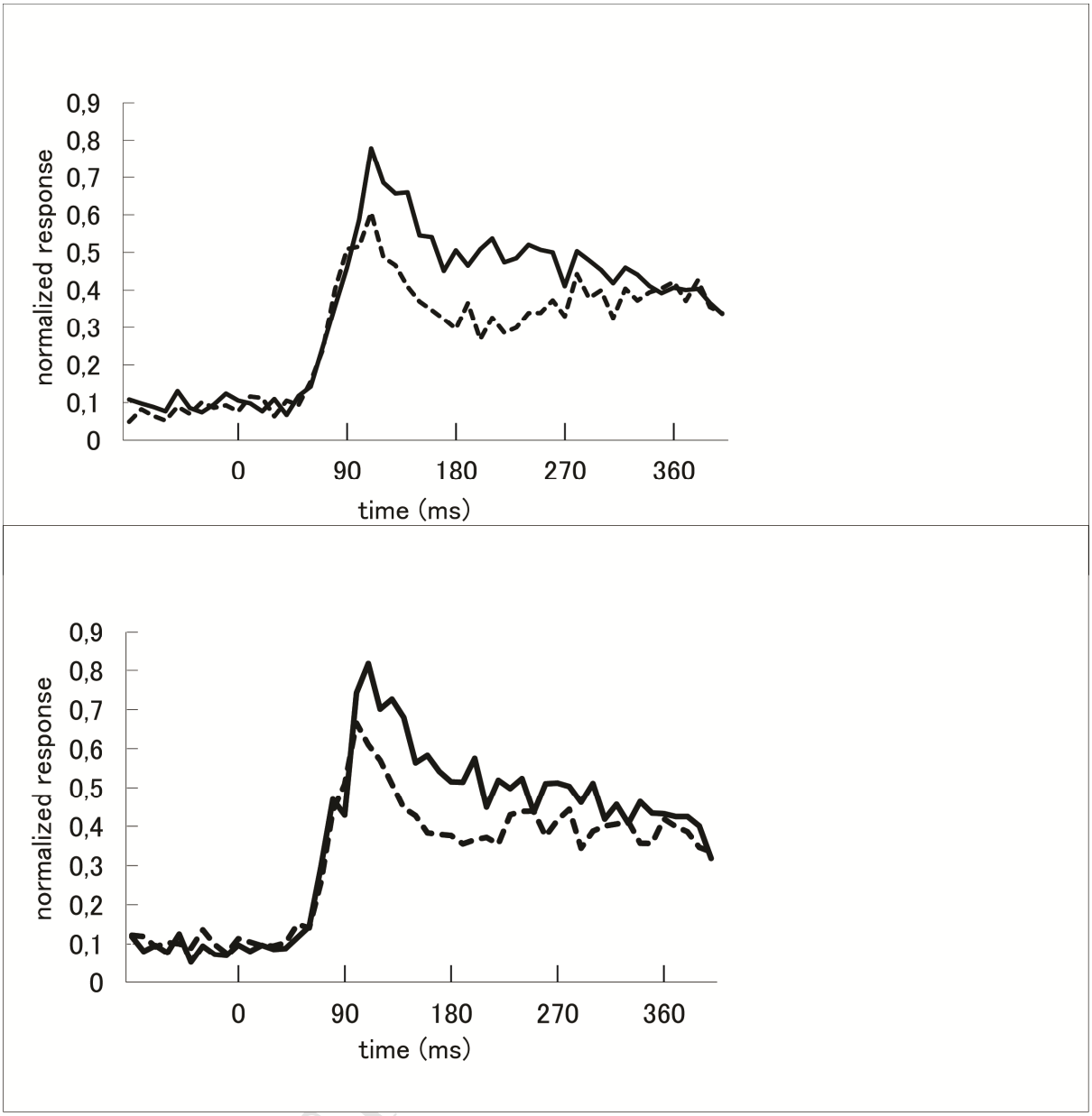

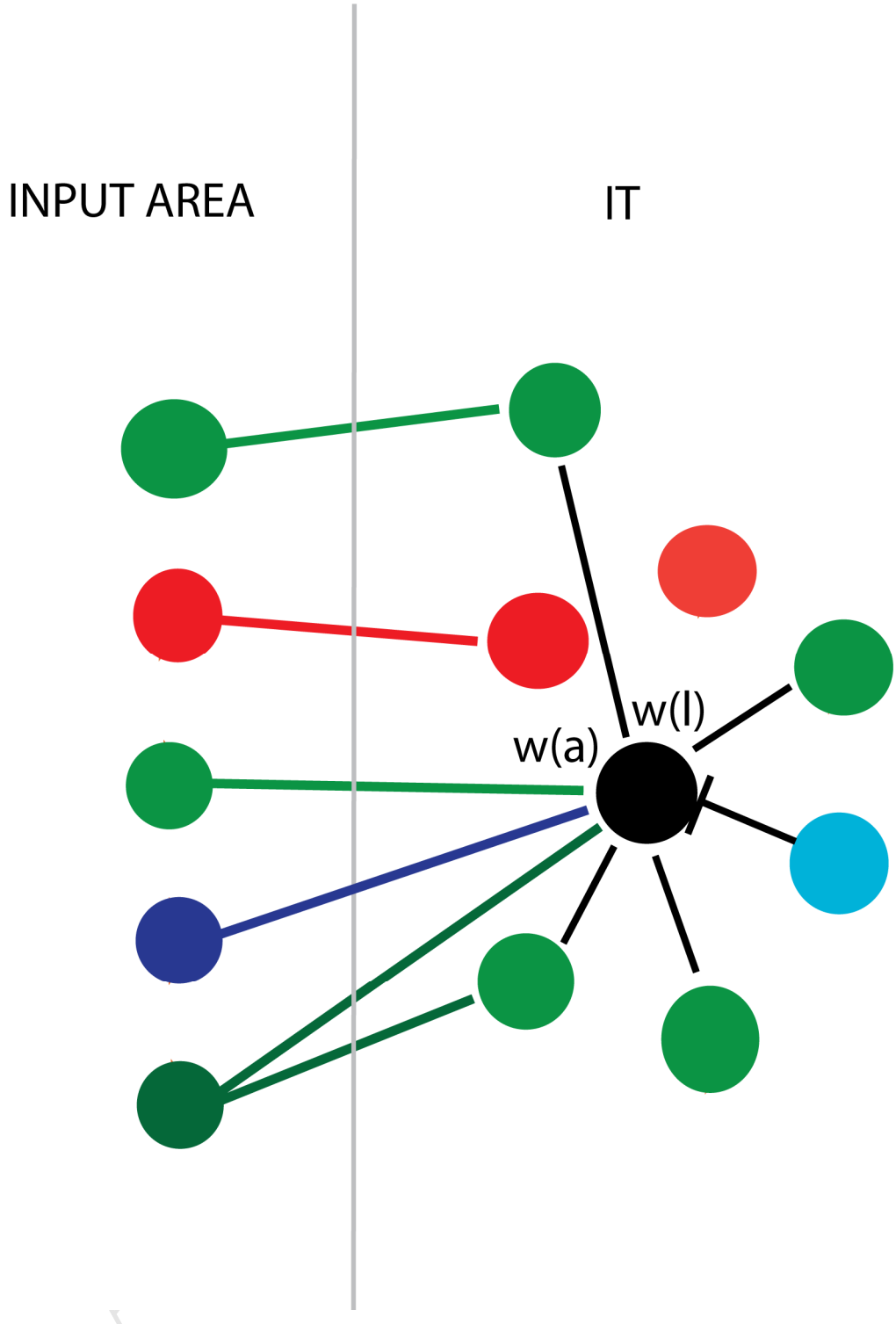
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